CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 040240

Trade Name : HYDROCODONE BITARTRATE AND ACETAMINOPHEN TABLETS USP

Generic Name: Hydrocodone Bitartrate and Acetaminophen Tablets USP 10mg/650mg and 7.5mg/650mg

Sponsor : Halsey Drug Company, Inc.

Approval Date: November 26, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 040240

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	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
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Medical Review(s)				
Chemistry Review(s)	X			
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Pharmacology Review(s)				
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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 040240

APPROVAL LETTER

ANDA 40-240

NOV 26 1997

Halsey Drug Company, Inc.
Attention: George F.J. Scholes
1827 Pacific St.
Brooklyn, NY 11233

Dear Sir:

This is in reference to your abbreviated new drug application dated January 3, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Hydrocodone Bitartrate and Acetaminophen Tablets USP, 10 mg/650 mg and 7.5 mg/650 mg.

Reference is also made to your amendments dated May 23, May 28, May 29, August 8, August 28, September 23, October 3, and November 5, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Hydrocodone Bitartrate and Acetaminophen Tablets USP, 10 mg/650 mg and 7.5 mg/650 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Hydrocodone Bitartrate and Acetaminophen Tablets USP; 10 mg/650 mg and 7.5 mg/650 mg, of Mikart, Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

11-26-97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040240

FINAL PRINTED LABELING

USUAL ADULT DOSAGE:
See package insert.

Store at controlled room temperature, 15°-30°C (59°-86°F).

HALSEY DRUG CO., INC.
Brooklyn, NY 11233 U.S.A.

NDC 0879-0778-10

HALSEY

III

HYDROCODONE* BITARTRATE and ACETAMINOPHEN TABLETS, USP

10 mg / 650 mg

Each tablet contains:
Hydrocodone* Bitartrate, USP ..... 10 mg
(***WARNING:** May be habit forming.)
Acetaminophen, USP ..... 650 mg

CAUTION: Federal law prohibits dispensing without prescription.

1000 TABLETS

Dispense in a tight, light-resistant container with a child-resistant closure.

Lot No./ Exp. See Container or Label.

0778 - 7/97

N 3 08790 77810 0

USUAL ADULT DOSAGE:
See package insert.

Store at controlled room temperature, 15°-30°C (59°-86°F).

HALSEY DRUG CO., INC.
Brooklyn, NY 11233 U.S.A.

NDC 0879-0778-05

HALSEY

III

HYDROCODONE* BITARTRATE and ACETAMINOPHEN TABLETS, USP

10 mg / 650 mg

Each tablet contains:
Hydrocodone* Bitartrate, USP ..... 10 mg
(***WARNING:** May be habit forming.)
Acetaminophen, USP ..... 650 mg

CAUTION: Federal law prohibits dispensing without prescription.

500 TABLETS

Dispense in a tight, light-resistant container with a child-resistant closure.

Lot No./ Exp. See Container or Label.

0778 - 7/97

N 3 08790 77805 6

USUAL ADULT DOSAGE:
See package insert.

Store at controlled room temperature, 15°-30°C (59°-86°F).

HALSEY DRUG CO., INC.
Brooklyn, NY 11233 U.S.A.

NDC 0879-0778-01

HALSEY

III

HYDROCODONE* BITARTRATE and ACETAMINOPHEN TABLETS, USP

10 mg / 650 mg

Each tablet contains:
Hydrocodone* Bitartrate, USP ..... 10 mg
(***WARNING:** May be habit forming.)
Acetaminophen, USP ..... 650 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 TABLETS

Dispense in a tight, light-resistant container with a child-resistant closure.

Lot No./ Exp. See Container or Label.

0778 - 7/97

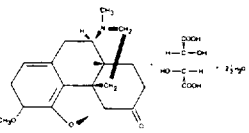
N 3 08790 77801 8

HYDROCODONE BITARTRATE & ACETAMINOPHEN TABLETS, USP 10mg/650mg

DESCRIPTION

Hydrocodone bitartrate and acetaminophen is supplied in tablet form for oral administration.

Hydrocodone bitartrate is an opioid analgesic and antitussive and occurs as fine, white crystals or as a crystalline powder. It is affected by light. Its chemical name is 4,5α-epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5). The structural formula of hydrocodone bitartrate is shown at right. Its molecular weight is 494.50 and molecular formula $C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2^1/_2H_2O$.



Acetaminophen, 4'-hydroxyacetanilide, a slightly bitter, white, odorless, crystalline powder, is a non-opiate, non-salicylate analgesic and anti-pyretic. Its structural formula is shown at right. Its molecular weight is 151.17 and molecular formula $C_8H_9NO_2$.

Each tablet contains:
Hydrocodone* Bitartrate, USP ..... 10 mg
(***Warning: May be habit forming**)
Acetaminophen, USP ..... 650 mg

Also contains: Croscarmellose Sodium, Anhydrous Lactose, Microcrystalline Cellulose, Povidone, Stearic Acid and Purified Water.

CLINICAL PHARMACOLOGY

Hydrocodone is a semisynthetic narcotic analgesic and antitussive with multiple actions qualitatively similar to those of codeine. Most of these involve the central nervous system and smooth muscle. The precise mechanism of action of hydrocodone and other opiates is not known, although it is believed to relate to the existence of opiate receptors in the central nervous system. In addition to analgesia, narcotics may produce drowsiness, changes in mood and mental clouding.

The analgesic action of acetaminophen involves peripheral influences, but the specific mechanism is as yet undetermined. Antipyretic activity is mediated through hypothalamic heat regulating centers. Acetaminophen inhibits prostaglandin synthetase. Therapeutic doses of acetaminophen have negligible effects on the cardiovascular or respiratory systems; however, toxic doses may cause circulatory failure and rapid, shallow breathing.

Pharmacokinetics: The behavior of the individual components is described below.

Hydrocodone: Following a 10 mg oral dose of hydrocodone administered to five adult male subjects, the mean peak concentration was 23.6 ± 5.2 ng/mL. Maximum serum levels were achieved at 1.3 ± 0.3 hours and the half-life was determined to be 3.8 ± 0.3 hours. Hydrocodone exhibits a complex pattern of metabolism including O-demethylation, N-demethylation and 6-keto reduction to the corresponding 6-α- and 6-β- hydroxymetabolites.

See OVERDOSAGE for toxicity information.

Acetaminophen: Acetaminophen is rapidly absorbed from the gastrointestinal tract and is distributed throughout most body tissues. The plasma half-life is 1.25 to 3 hours, but may be increased by liver damage and following overdosage. Elimination of acetaminophen is principally by liver metabolism (conjugation) and subsequent renal excretion of metabolites. Approximately 85% of an oral dose appears in the urine within 24 hours of administration, most as the glucuronide conjugate, with small amounts of other conjugates and unchanged drug.

See OVERDOSAGE for toxicity information.

INDICATIONS and USAGE

Hydrocodone and acetaminophen tablets are indicated for the relief of moderate to moderately severe pain.

CONTRAINDICATIONS

This product should not be administered to patients who have previously exhibited hypersensitivity to hydrocodone or acetaminophen.

WARNINGS

Respiratory Depression: At high doses or in sensitive patients, hydrocodone may produce dose-related respiratory depression by acting directly on the brain stem respiratory center. Hydrocodone also affects the center that controls respiratory rhythm, and may produce irregular and periodic breathing.

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a preexisting increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute Abdominal Conditions: The administration of narcotics may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

PRECAUTIONS

General: Special Risk Patients: As with any narcotic analgesic agent, hydrocodone bitartrate and acetaminophen tablets should be used with caution in elderly or debilitated patients, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy or urethral stricture. The usual precautions should be observed and the possibility of respiratory depression should be kept in mind.

Cough Reflex: Hydrocodone suppresses the cough reflex; as with all narcotics, caution should be exercised when hydrocodone bitartrate and acetaminophen tablets are used postoperatively and in patients with pulmonary disease.

Information for Patients: Hydrocodone, like all narcotics, may impair mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery; patients should be cautioned accordingly.

Alcohol and other CNS depressants may produce an additive CNS depression, when taken with this combination product, and should be avoided.

Hydrocodone may be habit-forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.

Laboratory Tests: In patients with severe hepatic or renal disease, effects of therapy should be monitored with serial liver and/or renal function tests.

Drug Interactions: Patients receiving narcotics, antihistamines, antipsychotics, antianxiety agents, or other CNS depressants (including alcohol) concomitantly with hydrocodone bitartrate and acetaminophen tablets may exhibit an additive CNS depression. When combined therapy is contemplated, the dose of one or both agents should be reduced.

The use of MAO inhibitors or tricyclic antidepressants with hydrocodone preparations may increase the effects of either the antidepressant or hydrocodone.

Drug/Laboratory Test Interactions: Acetaminophen may produce false-positive test results for urinary 5-hydroxyindoleacetic acid.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No adequate studies have been conducted in animals to determine whether hydrocodone or acetaminophen have a potential for carcinogenesis, mutagenesis, or impairment of fertility.

Pregnancy:
Teratogenic Effects: Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. Hydrocodone bitartrate and acetaminophen tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose. There is no consensus on the best method of managing withdrawal.

Labor and Delivery: As with all narcotics, administration of this product to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used.

Nursing Mothers: Acetaminophen is excreted in breast milk in small amounts, but the significance of its effects on nursing infants is not known. It is not known whether hydrocodone is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from hydrocodone and acetaminophen, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

The most frequently reported adverse reactions are lightheadedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include:

Central Nervous System: Drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, psychic dependence, mood changes.

Gastrointestinal System: Prolonged administration of hydrocodone bitartrate and acetaminophen tablets may produce constipation.

Genitourinary System: Ureteral spasm, spasm of vesical sphincters and urinary retention have been reported with opiates.

Respiratory Depression: Hydrocodone bitartrate may produce dose-related respiratory depression by acting directly on brain stem respiratory centers (see OVERDOSAGE).

Dermatological: Skin rash, pruritus.

The following adverse drug events may be borne in mind as potential effects of acetaminophen: allergic reactions, rash, thrombocytopenia, agranulocytosis.

Potential effects of high dosage are listed in the overdosage section.

DRUG ABUSE and DEPENDENCE

Controlled Substance: Hydrocodone Bitartrate and Acetaminophen Tablets are classified as a Schedule III controlled substance.

Abuse and Dependence: Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of narcotics; therefore, this product should be prescribed and administered with caution. However, psychic dependence is unlikely to develop when hydrocodone bitartrate and acetaminophen tablets are used for a short time for the treatment of pain.

Physical dependence, the condition in which continued administration of the drug is required to prevent the appearance of a withdrawal syndrome, assumes clinically significant proportions only after several weeks of continued narcotic use, although some mild degree of physical dependence may develop after a few days of narcotic therapy. Tolerance, in which increasingly large doses are required in order to produce the same degree of analgesia, is manifested initially by a shortened duration of analgesic effect, and subsequently by decreases in the intensity of analgesia. The rate of development of tolerance varies among patients.

OVERDOSAGE

Following an acute overdosage, toxicity may result from hydrocodone or acetaminophen.

Signs and Symptoms:

Hydrocodone: Serious overdose with hydrocodone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur.

Acetaminophen: In acetaminophen overdosage: dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma and thrombocytopenia may also occur.

Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

In adults, hepatic toxicity has rarely been reported with acute overdoses of less than 10 grams or fatalities with less than 15 grams.

Treatment: A single or multiple overdose with hydrocodone and acetaminophen is a potentially lethal polydrug overdose, and consultation with a regional poison control center is recommended.

Immediate treatment includes support of cardiorespiratory function and measures to reduce drug absorption. Vomiting should be induced mechanically, or with syrup of ipecac, if the patient is alert (adequate pharyngeal and laryngeal reflexes). Oral activated charcoal (1 g/kg) should follow gastric emptying. The first dose should be accompanied by an appropriate cathartic. If repeated doses are used, the cathartic might be included with alternate doses as required. Hypotension is usually hypovolemic and should respond to fluids. Vasopressors and other supportive measures should be employed as indicated. A cuffed endo-tracheal tube should be inserted before gastric lavage of the unconscious patient and, when necessary, to provide assisted respiration.

Meticulous attention should be given to maintaining adequate pulmonary ventilation. In severe cases of intoxication, peritoneal dialysis, or preferably hemodialysis may be considered. If hypoprothrombinemia occurs due to acetaminophen overdose, vitamin K should be administered intravenously.

Naloxone, a narcotic antagonist, can reverse respiratory depression and coma associated with opioid overdose. Naloxone hydrochloride 0.4 mg to 2 mg is given parenterally. Since the duration of action of hydrocodone may exceed that of the naloxone, the patient should be kept under continuous surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration. A narcotic antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

If the dose of acetaminophen may have exceeded 140 mg/kg, acetylcysteine should be administered as early as possible. Serum acetaminophen levels should be obtained, since levels four or more hours following ingestion help predict acetaminophen toxicity. Do not await acetaminophen assay results before initiating treatment. Hepatic enzymes should be obtained initially, and repeated at 24-hour intervals.

Methemoglobinemia over 30% should be treated with methylene blue by slow intravenous administration.

The toxic dose for adults for acetaminophen is 10 g.

DOSAGE and ADMINISTRATION

Dosage should be adjusted according to severity of pain and response of the patient. However, it should be kept in mind that tolerance to hydrocodone can develop with continued use and that the incidence of untoward effects is dose related.

The usual adult dosage is one tablet every four to six hours as needed for pain. The total daily dosage should not exceed 6 tablets.

HOW SUPPLIED

Hydrocodone Bitartrate **(Warning: May be habit forming)** and Acetaminophen Tablets USP, 10 mg/650 mg are white, capsule shaped, scored tablets, debossed with HD 778. They are packaged in bottle sizes of 100, 500 and 1000.

Store at controlled room temperature 15-30° C (59-86° F).

Dispense in a tight, light-resistant container with child-resistant closure.

Caution: Federal law prohibits dispensing without prescription.

Manufactured by
HALSEY DRUG CO., INC.
Brooklyn, NY 11233-3599 U.S.A.

Revised 08/97
K.T.

08790778

HYDROCODONE BITARTRATE & ACETAMINOPHEN TABLETS, USP 10mg / 650mg

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040240

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 40-240

3. NAME AND ADDRESS OF APPLICANT
Halsey Drug Company, Inc.
1827 Pacific St.
Brooklyn, NY 11233

4. LEGAL BASIS FOR SUBMISSION
Certify to the best of their knowledge there are no patents that claim the listed drug product and referenced listed drug is not entitled to a period of marketing exclusivity.
Listed Product:
Mikart, Inc. - Lorcet® 10 mg/650 mg
Mikart, Inc. - Lorcet Plus® 7.5 mg/650 mg

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
None

7. NONPROPRIETARY NAME
Hydrocodone Bitartrate and Acetaminophen

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Firm:
- 1/3/97 - Original.
- 5/16/97 - Withdrawal of ANDA 40-242.
- 5/23/97 - Amendment, response to 3/10/97 request to withdraw letter.
- 5/28/97 - Amendment, response to 3/10/97 address exclusivity letter.
- 5/29/97 - O/NC, request for global review of ANDA 40-236 and 40-240, not granted 6/5/97.
- 6/9/97 - O/NC, independent application audit.
- 8/8/97 - Response to 1st def. facsimile (chem. & labeling. Subject of this review.
- 8/28/97 - Response to 2nd def. facsimile (labeling). Subject of this review.
- 9/23/97 - Response to phone memo. Subject of this review.
- 10/3/97 - O/NC, revised batch record (10/650) to include moisture adjustment. Subject of this review.
- 11/5/97 - Response to phone memo. Subject of this review.

FDA:
- 3/10/97 - Acknowledgment, address exclusivity.
- 3/10/97 - Letter requesting firm to withdraw ANDA 40-242 (7.5 mg/650 mg) and submit as amendment to ANDA 40-240.
- 6/23/97 - Bio. review, acceptable (10 mg/650 mg).
- 6/30/97 - Bio. letter, no further questions at this time (10 mg/650 mg).
- 7/31/97 - 1st def. facsimile (chem. & labeling).
- 8/18/97 - Bio, review, acceptable (7.5 mg/650 mg).
- 8/20/97 - Bio. letter, no further questions at this time (7.5 mg/650 mg).

8/25/97 - 2nd def. facsimile (labeling).
9/22/97 - Phone memo, add *p*-amino phenol to finished product and stability.
11/3/97 - Phone memo, need to revised batch record (7.5/650) to include moisture adjustment.

10. PHARMACOLOGICAL CATEGORY
Narcotic Analgesic

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

(b)4 - Confidential Business

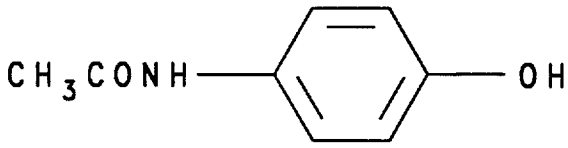
13. DOSAGE FORM
Tablet

14. POTENCY
10 mg/650 mg & 7.5 mg/650 mg

15. CHEMICAL NAME AND STRUCTURE

Acetaminophen USP

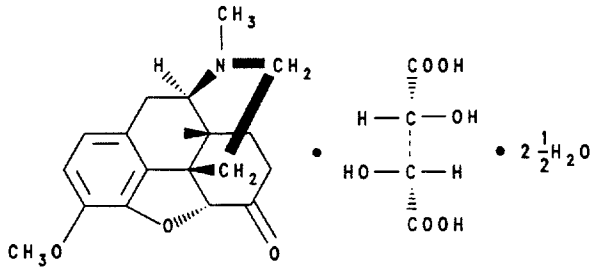
$C_8H_9NO_2$; M.W. = 151.16



4'-Hydroxyacetanilide. CAS [103-90-2]

Hydrocodone Bitartrate USP

$C_{18}H_{21}NO_3 . C_4H_6O_6 . 2\frac{1}{2}H_2O$; M.W. = 494.50



4,5α-Epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5). CAS [34195-34-1; 6190-38-1]

16. RECORDS AND REPORTS
N/A

17. COMMENTS
a. EER sent on 2/19/97, pending.

Method validation not needed, product is USP. DMF's, labeling, and Bio. are satisfactory.

18. CONCLUSIONS AND RECOMMENDATIONS
Approval

19. REVIEWER: Norman Gregory

DATE COMPLETED:
10/6/97 (chem.)
9/5/97 (labeling)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040240

BIOEQUIVALENCE REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #40-240
SPONSOR: Halsey Drug Company, Inc.
DRUG: Hydrocodone Bitartrate; Acetaminophen Tablets 7.5 mg/650 mg
DOSAGE FORM: Tablets
STRENGTH: 7.5 mg/650 mg
REFERENCE PRODUCT: Mikart's Hydrocodone Bitartrate; Acetaminophen Tablets 7.5 mg/650 mg.
SUBMISSION TYPE: Waiver

STUDY SUMMARY: Not Applicable

DISSOLUTION: Not Applicable

WAIVER SUMMARY: The waiver of the *in vivo* bioequivalence study for the test product, Hydrocodone Bitartrate; Acetaminophen Tablets 7.5 mg/650 mg is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test product formulation to be bioequivalent to the reference drug Mikart's Hydrocodone Bitartrate; Acetaminophen Tablets 7.5 mg/650 mg.

PRIMARY REVIEWER: Zakaria Wahba, Ph.D. BRANCH: III

INITIAL: /S/ DATE: 11/24/97

GROUP LEADER: Ramakant Mhatre, Ph.D. BRANCH: III

for

INITIAL: /S/ DATE: 11/24/1997

ACTING DIRECTOR: Rabindra Patnaik, Ph.D.
DIVISION OF BIOEQUIVALENCE

INITIAL: /S/ DATE: 11/24/97

DIRECTOR
OFFICE OF GENERIC DRUGS

INITIAL: _____ DATE: _____

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #40-240
SPONSOR: Halsey Drug Company, Inc.
DRUG: Hydrocodone Bitartrate; Acetaminophen Tablets 10 mg/650 mg
DOSAGE FORM: Tablets
STRENGTH: 10 mg/650 mg
REFERENCE PRODUCT: Mikart's Lorcet® Tablets 10 mg/650 mg.
SUBMISSION TYPE: Waiver

STUDY SUMMARY: Not Applicable

DISSOLUTION: Not Applicable

WAIVER SUMMARY: The waiver of the *in vivo* bioequivalence study for the test product, Hydrocodone Bitartrate; Acetaminophen Tablets 10 mg/650 mg is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test product formulation to be bioequivalent to the reference drug Mikart's Lorcet® Tablets 10 mg/650 mg.

PRIMARY REVIEWER: Zakaria Wahba, Ph.D. BRANCH: III

INITIAL: /S/ DATE: 6/17/1997

GROUP LEADER: Ramakant Mhatre, Ph.D. BRANCH: III

INITIAL: /S/ DATE: 6/18/97

DIRECTOR: Nicholas Fleischer, Ph.D.
DIVISION OF BIOEQUIVALENCE

INITIAL: /S/ DATE: 6/24/97

DIRECTOR
OFFICE OF GENERIC DRUGS

INITIAL: DATE:

AUG 18 1997

Hydrocodone Bitartrate;
Acetaminophen Tablets
7.5 mg/650 mg
ANDA #**40-240**
Reviewer: Z.Z. Wahba
wp# 40240w2.597

Halsey Drug Company, Inc.
Brooklyn, N.Y.
Submission Date:
May 23, 1997
May 29, 1997

REVIEW OF A WAIVER REQUEST
FOR A NEW STRENGTH

I. BACKGROUND

1. The firm has submitted comparative in vitro dissolution data for its test drug product, Hydrocodone Bitartrate; Acetaminophen Tablets 7.5 mg/650 mg, and the reference listed product, Mikart's Hydrocodone Bitartrate; Acetaminophen Tablets 7.5 mg/650 mg under the trade name Larked® Plus (NDA #89-689).

2. The firm has previously submitted comparative in vitro dissolution data for its test drug product, Hydrocodone Bitartrate; Acetaminophen Tablets 10 mg/650 mg, and the reference listed product, Mikart's Hydrocodone Bitartrate; Acetaminophen Tablets 10 mg/650 mg under the trade name Lorcet® (NDA #81-223). The waiver request for the 10 mg/650 mg strength was granted (June 23, 1997).

3. The drug product is classified "AA" in the list of the "Approved Drug Products with Therapeutic Equivalence Evaluations".

II. FORMULATION COMPARISON

The formulation comparison statement was given on page #110, vol. #B2.1, ANDA 40-240.

No	Ingredients	Test mg/tablet
1	Hydrocodone Bitartrate, USP	7.5
2	Acetaminophen Powder USP	650
3	Croscarmellose Sodium [redacted] NF	[redacted]
4	Microcrystalline Cellulose [redacted] NF	(b)4 - Confidential Business
5	Lactose Anhydrous DT, NF	
6	Povidone [redacted] USP	[redacted]
7	Stearic Acid, NF	

8	Purified Water	Q.S.

Note: The reference product contains the following inactive ingredients: Colloidal silicon dioxide, Croscarmellose sodium, Crospovidone, Microcrystalline Cellulose, Povidone, Pregelatinized starch and Stearic acid.

III. DISSOLUTION

The firm has submitted dissolution data for its drug product, Hydrocodone Bitartrate; Acetaminophen, 7.5 mg/650 mg tablets, applying the following conditions:

Method: USP 23 apparatus II (Paddle) at 50 rpm
Medium: 900 ml PO_4, pH 5.8 buffer
Temperature: 37°C ± 0.5°C
Number of Tablets: 12
Specification: NLT (b)4 in 30 minutes
Reference product: Hydrocodone Bitartrate; Acetaminophen, 7.5 mg/650 mg manufactured by Mikart Inc. under the trade name LORCET® Plus.
Method of Dissolution: USP method

Table 1. In Vitro Dissolution Testing

Drug (Generic Name): Hydrocodone Bitartrate; Acetaminophen
Dose Strength: 7.5 mg/650 mg
ANDA No.: 40240
Firm: Halsey Drug Company, Inc.
Submission Date: May 23, 1997
File Name: 40240w2.597

I. Conditions for Dissolution Testing:

USP 23 Method Basket: Paddle: X RPM: 50
No. Units Tested: 12 Tablets
Medium: PO_4 Buffer pH 5.8 Volume: 900 mL
Specifications: NLT (b)4 is dissolved in 30 minutes
Reference Drug: Hydrocodone Bitartrate; Acetaminophen 10 mg/650 mg manufactured by Mikart
Assay Methodology: (b)4 - Confidential

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product: Acetaminophen Lot #960501 Strength(mg) 650			Reference Product: Acetaminophen Lot #950816G Strength(mg) 650		
	Mean %	Range	%CV	Mean %	Range	%CV
10	85	(b)4 -	6.6	100	(b)4 -	1.2

20	96	(b)4 - Confidentia	4.2	100	(b)4 - Confidentia	1.0
30	98		2.4	100		0.9

Sampling Times (Minutes)	Test Product: Hydrocodone Bitartrate Lot #960501 Strength(mg) 7.5			Reference Prod.:Hydrocodone Bitartrate Lot #950816G Strength(mg) 7.5		
	Mean %	Range	%CV	Mean %	Range	%CV
10	92	(b)4 - Confidentia Business	5.7	101	(b)4 - Confidentia Business	1.7
20	100		2.7	100		1.2
30	100		2.0	100		1.1

Assay and Content Uniformity Data:
Test Product (lot #960501)

	Hydrocodone Bitartrate	Acetaminophen
Content Uniformity	100.0%	100.6%
Assay Potency	100.6%	101.2%

IV. COMMENTS

1. The drug product is classified "AA" in the list of the "Approved Drug Products with Therapeutic Equivalence Evaluations".

2. The test drug product contains the same active ingredients in the same strength and dosage form as the currently approved listed reference product.

3. The test drug product contains no inactive ingredient(s) that is known to significantly affect absorption of the active drug ingredient or therapeutic moiety.

4. The concentrations that are provided in the statement of chemical composition for all the inactive ingredients fall within the acceptable range of the Agency's Inactive Ingredient Guide.

5. The dissolution data for the test product is acceptable.

6. The waiver of in vivo bioequivalence study requirements may be granted based on 21 CFR section 320.22(c) of the Bioavailability/Bioequivalence Regulations.

V. RECOMMENDATION

1. The Division of Bioequivalence agrees that the information

submitted by Halsey Drug Company, Inc. on its drug product, Hydrocodone Bitartrate; Acetaminophen Tablets 7.5 mg/650 mg falls under 21 CFR section 320.22(c) of the Bioavailability/Bioequivalence Regulations. The waiver of in vivo bioequivalence study for the drug is granted. From the Bioequivalence point of view, the Division of Bioequivalence deems the firm's test product, Hydrocodone Bitartrate; Acetaminophen Tablets 7.5 mg/650 mg is deemed bioequivalent to the reference listed product, Mikart's Hydrocodone Bitartrate; Acetaminophen Tablets 7.5 mg/650 mg.

2. The dissolution testing conducted by Halsey Drug Company, Inc. on its drug product, Hydrocodone Bitartrate; Acetaminophen Tablets 7.5 mg/650 mg is acceptable.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml of PO_4 Buffer pH 5.8, at 37°C using Apparatus II (Paddle) at 50 rpm. The test product should meet the following specifications:

   Not less than (b)4 of both active components of the labeled amount of the drug is dissolved in 30 minutes.

The firm should be informed of the recommendation.

/S/

Zakaria Z. Wahba, Ph.D.
Review Branch III
Division of Bioequivalence

RD INITIALED RMHATRE /S/ 7/25/97
FT INITIALED RMHATRE

Concur: /S/ Date: 8/18/1997
Nicholas Fleischer, PH.D.
Director
Division of Bioequivalence

cc: ANDA 40-240 (original, duplicate), HFD-630, HFD-658 (Mhatre, Wahba), HFD-650 (Director), Drug File, Division File
ZZWahba/071597/072397/file #40240w2.597

ANDA 40-240

AUG 20 1997

Halsey Drug Company, Inc.
Attention: George F.J. Scholes
1827 Pacific Street
Brooklyn NY 11233

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Hydrocodone Bitartrate and Acetaminophen Tablets USP, 7.5 mg/650 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 40-240

Halsey Drug Company, Inc.
Attention: George F.J. Scholes
1827 Pacific Street
Brooklyn NY 11233

JUN 30 1997

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Hydrocodone Bitartrate and Acetaminophen Tablets USP, 10 mg/650 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

JUN 23 1997

Hydrocodone Bitartrate; Acetaminophen Tablets
10 mg/650 mg
ANDA #**40-240**
Reviewer: Z.Z. Wahba
wp# 40240w.197

Halsey Drug Company, Inc.
Brooklyn, N.Y.
Submission Date:
January 03, 1997

REVIEW OF DISSOLUTION DATA AND A WAIVER REQUEST

I. BACKGROUND

1. The firm has submitted comparative in vitro dissolution data for its test drug product, Hydrocodone Bitartrate; Acetaminophen Tablets 10 mg/650 mg, and the reference listed product, Mikart's Hydrocodone Bitartrate; Acetaminophen Tablets 10 mg/650 mg under the trade name Lorcet® (NDA #81-223).

2. The drug product is classified "AA" in the list of the "Approved Drug Products with Therapeutic Equivalence Evaluations".

II. FORMULATION COMPARISON

The formulation comparison statement was given on page #133, vol. #B1.1, ANDA 40-240.

No	Ingredients	Test mg/tablet
1	Hydrocodone Bitartrate, USP	10
2	Acetaminophen Powder USP	650
3	Croscarmellose Sodium NF	[redacted]
4	Microcrystalline Cellulose [redacted] NF	[redacted] (b)4 - Confident Busines
5	Lactose Anhydrous DT, NF	[redacted]
6	Providone, USP, K-90	[redacted]
7	Stearic Acid, NF	[redacted]
8	Purified Water, USP	Q.S.

Note: The reference product contains the following inactive ingredients: Croscarmellose sodium, Lactose Anhydrous, Microcrystalline Cellulose, Povidone and water.

III. DISSOLUTION

The firm has submitted dissolution data for its drug product, Hydrocodone Bitartrate; Acetaminophen, 10 mg/650 mg tablets, applying the following conditions:

Method: USP 23 apparatus II (Paddle) at 50 rpm
Medium: 900 ml PO_4, pH 5.8 buffer
Temperature: 37°C ± 0.5°C
Number of Tablets: 12
Specification: NLT (b)(4) in 30 minutes
Reference product: Hydrocodone Bitartrate; Acetaminophen, 10 mg/650 mg manufactured by Mikart Inc. under the trade name LORCET®.
Method of Dissolution: USP method

Table 1. In Vitro Dissolution Testing

Drug (Generic Name): Hydrocodone Bitartrate; Acetaminophen
Dose Strength: 10 mg/650 mg
ANDA No.: 40240
Firm: Halsey Drug Company, Inc.
Submission Date: January 03, 1997
File Name: 40240w.197

I. Conditions for Dissolution Testing:

USP 23 Method Basket: Paddle: X RPM: 50
No. Units Tested: 12 Tablets
Medium: PO_4 Buffer pH 5.8 Volume: 900 mL
Specifications: NLT (b)(4) is dissolved in 30 minutes
Reference Drug: Hydrocodone Bitartrate; Acetaminophen 10 mg/650 mg manufactured by Mikart.
Assay Methodology (b)(4)

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product: Acetaminophen Lot #960503 Strength(mg) 650			Reference Product: Acetaminophen Lot #950666F Strength(mg) 650		
	Mean %	Range	%CV	Mean %	Range	%CV
10	80	(b)(4) - Confidential Business	7.7	101	(b)(4) - Confidential Business	0.8
20	98		1.8	101		1.0
30	101		0.7	101		0.9

Sampling Times (Minutes)	Test Product: Hydrocodone Bitartrate Lot #960503 Strength(mg) 10	Reference Product: Hydrocodone Bitartrate Lot #950666F Strength(mg) 10

	Mean %	Range	%CV	Mean %	Range	%CV
10	89	(b)4 - Confidential Business	7.3	102	(b)4 - Confidential Business	1.4
20	103		1.4	102		1.6
30	104		1.0	103		1.8

Assay and Content Uniformity Data:

Test Product (lot #960503)

	Hydrocodone Bitartrate	Acetaminophen
Content Uniformity	101.0% (%CV=0.9)	100.2% (%CV=0.7)
Assay Potency	102% (%CV=1.0)	101% (%CV=1.1)

IV. COMMENTS

1. The drug product is classified "AA" in the list of the "Approved Drug Products with Therapeutic Equivalence Evaluations".

2. The test drug product contains the same active ingredients in the same strength and dosage form as the currently approved listed reference product.

3. The test drug product contains no inactive ingredient(s) that is known to significantly affect absorption of the active drug ingredient or therapeutic moiety.

4. The concentrations that are provided in the statement of chemical composition for all the inactive ingredients fall within the acceptable range of the Agency's Inactive Ingredient Guide.

5. The dissolution data for the test product is acceptable.

6. The waiver of in vivo bioequivalence study requirements may be granted based on 21 CFR section 320.22(e) of the Bioavailability/Bioequivalence Regulations.

V. RECOMMENDATION

1. The Division of Bioequivalence agrees that the information submitted by Halsey Drug Company, Inc. on its drug product, Hydrocodone Bitartrate; Acetaminophen Tablets 10 mg/650 mg falls under 21 CFR section 320.22(e) of the Bioavailability/Bioequivalence Regulations. The waiver of in vivo bioequivalence study for the drug is granted. From the Bioequivalence point of view, the Division of Bioequivalence deems the firm's test product, Hydrocodone Bitartrate; Acetaminophen Tablets 10 mg/650 mg is deemed bioequivalent to the reference listed product, Mikart's Hydrocodone Bitartrate; Acetaminophen Tablets 10 mg/650 mg.

2. The dissolution testing conducted by Halsey Drug Company, Inc. on its drug product, Hydrocodone Bitartrate; Acetaminophen Tablets 10 mg/650 mg is acceptable.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml of PO_4 Buffer pH 5.8, at 37°C using Apparatus II (Paddle) at 50 rpm. The test product should meet the following specifications:

   Not less than (b)(4) of both active components of the labeled amount of the drug is dissolved in 30 minutes.

The firm should be informed of the recommendation.

/S/

Zakaria Z. Wahba, Ph.D.
Review Branch III
Division of Bioequivalence

RD INITIALED RMHATRE /S/ 6/18/97
FT INITIALED RMHATRE

Concur: /S/ Date: 6/23/97
Nicholas Fleischer, Ph.D.
Director
Division of Bioequivalence

cc: ANDA 40-240 (original, duplicate), HFD-630, HFD-658 (Mhatre, Wahba), HFD-650 (Director), Drug File, Division File
ZZWahba/051997/61797/file #40240w.197